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Combine social and population health science approaches to understand the human microbiome

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Abstract

The microbiome is now considered our 'second genome' with potentially comparable importance to the genome in determining human health. There is, however, a relatively limited understanding of the broader environmental factors, particularly social conditions that shape variation in human microbial communities. Fulfilling the promise of microbiome research—particularly the microbiome's potential for modification—will require collaboration between biologists and social and population scientists. For life scientists, the plasticity and adaptiveness of the microbiome calls for an agenda to understand the sensitivity of the microbiome to broader social environments already known to be powerful predictors of morbidity and mortality. For social and population scientists, attention to the microbiome may help elucidate nagging questions as to the underlying biological mechanisms that link social conditions to health. We outline key substantive and methodological advances that can be made if collaborations between social and population health scientists and life scientists are strategically pursued.

We are an amalgamation of cells, both human and microbial, and there is growing evidence that the trillions of microbes that inhabit the human body—collectively referred to as the human microbiota—have profound implications for human health [1]. This complex human ecosystem belies the traditional dichotomy between "good" and "bad" bacteria, giving way to a more nuanced consideration of changing and interacting networks of microbes. The microbiome is now considered our 'second genome' with potentially larger importance than the genome in shaping human health [2]. What makes the microbiome potentially so pivotal for shaping health—and potentially of significant interest to social science and population health researchers—is its plasticity, or ability to be altered, and, specifically, its responsiveness to the environment [3]. Yet, despite rapid technological progress in description and sequencing, gaps remain in our understanding of the broader environmental factors that shape inter-individual variation in these microbial communities [4], particularly in regards to how social conditions may influence this variation.

We argue that fulfilling the promise of microbiome research—particularly the human microbiome's potential for modification—will require closer collaboration between life scientists and social and population health scientists who can consider the interaction of multiple levels of environmental exposures. The very nature of the microbiome, particularly its plasticity and adaptiveness to the environment, opens the door to a broader research agenda focused on how social conditions influence the microbiome. For analytic purposes, we focus on early life conditions, socioeconomic resources, and social relationships as cases studies for the possibilities these collaborations may hold. Decades of experimental and observational evidence demonstrate these conditions influence morbidity and mortality at levels far exceeding individual behaviors like obesity or even medical interventions like anti-hypertensives. For social and population scientists, attention to the microbiome may help elucidate nagging questions as to the underlying biological mechanisms that link social conditions to health, and promote attention to policy and other upstream factors that drive changes in the microbiome at the population level.

In this paper, we first detail existing research on how social environments influence the gut microbiome, focusing especially on early life conditions, socioeconomic factors and social relationships. We then outline potential interdisciplinary collaborations across these three substantive areas, detailing ways in which existing population based studies and methods could be employed to test novel hypotheses about the human gut microbiome. In sum, we detail key substantive and methodological advances that can be made if collaborations between the social and population sciences and life sciences are strategically pursued, with a particular, though not exclusive, emphasis on the gut microbiome, where the largest number of microbial communities in the human body can be found.

Existing Research on Social Environments and Gut Microbiome

The gastrointestinal tract is estimated to harbor roughly 90% of our indigenous microbes [5]. There is increasing empirical evidence, both from animal and human population studies, that distal gut community patterns play an important role in a broad range of physiological functions of their host, including immune system maturation, metabolic and inflammatory processes, and even the brain and behavior via the 'gut-brain axis' [6]. Indeed, the gut microbiota is now implicated in a wide array of chronic diseases, including type-1 and type-2 diabetes, inflammatory bowel disease, obesity, cardiovascular disease, and cancer, which remain among the leading causes of morbidity and mortality in the developed-and increasingly developing-world [1,2]. Moreover, there is a robust body of research demonstrating how diet and nutritional factors influence the gut microbiome, which may prove a key pathway linking diet to health. [7] The rapid acceleration of research-including successful clinical interventions involving fecal transplants-points to the general consensus that the gut microbiome could radically transform research and interventions to improve human health.

Despite large advances, however, scientific knowledge of the gut microbiome—especially the way broader environments shape its variability over the life course—remains in its infancy. Research is still limited regarding how broader social environments and conditions shape exposures and ultimately influence its composition, especially research employing human subjects. This limitation is important because recent

evidence demonstrated that the environment—rather than genetics—predominantly shapes human gut microbial composition [8]. How this "environment" is defined and measured has not yet been well developed. Yet, a small, but growing body of literature is looking at how our social environment shapes acquisition and exchange of microbes—from the people we interact with to the environments in which we work and live? [9-13]. In the section below, we explore existing research that touches on how our social environments, specifically early life conditions, social relationships, and socioeconomic conditions, may shape the human gut microbiome [9]. Figure 1 outlines a general conceptual framework for potential pathways linking social environments and the microbiome over the life course, some of which we highlight below.

[Insert Figure 1 Here]

Early life Conditions

It is well known that birth and early life are critical periods for the acquisition and development of an individual's microbiome. Broadly, prenatal and early life environments play an important role in developmental trajectories for both the immune and stress response systems, with implications for developing microbiota as well [14-16]. Since humans are born mostly (albeit not fully) microbially sterile, it is necessarily through interaction with the social and physical environment around them that subsequent microbial colonization takes place. Specifically, exposures such as mode of delivery and initiation and duration of breastfeeding influence its composition, and these early life exposures are in turn shaped by one's social status [17-19]. The quality of fetal environments—such as proper nutrition—is strongly patterned by income and education, including in the developed world [20-22]. This remains true after birth. While 91 percent of mothers with a college degree breast feed in the U.S., that rate falls to 69 percent for mothers with a high school degree. These rates fall to 28 percent and 14 percent for 6 months of exclusive breastfeeding [23].

We are beginning to see evidence that the lack of healthy microbiome development in children can have severe and lasting consequences. [24] For example, evidence from fecal transplant studies in mice show that the microbiomes of undernourished children negatively affect physical and cognitive development [23,25]. Despite this

evidence of how extreme malnutrition in early life in the developing world alters the developing microbiome, we have little evidence from the developed world regarding how variation in early life socioeconomic resources influences the developing gut microbiome.

Social Relationships

Social relationships have long been linked to health and mortality, including inflammation and immune response [22]. Indeed, the evidence is that the influence of social relationships on health and mortality exceeds medical interventions such as quitting smoking and the use of anti-hypertensives, like statins [26]. Given the robustness of this relationship, and the links between social relationships and inflammation and immune functioning, it is not surprising that research is now beginning to explore whether and how social interactions shape the microbiome.

In terms of existing research, studies using primate models suggest that social relationships impact the composition of the gut microbiota through direct microbial sharing between individuals [27-30]. Tung and colleagues, for example, found that social network and social group predicted the species in the gut microbiome of 48 wild baboons, even after adjusting for other shared factors including kinship, diet, and shared environments, suggesting the importance of direct physical contact during social interactions in transmitting gut microbiomes. A few human studies have begun to document these relationships. For example, two recent studies found that individuals living together had more similar gut [18] and skin [18,19] microbiota than did those living apart. Some even hypothesize that microbes can help explain the evolution of social behaviors [31]; the effect of microbiota on the hosts' central nervous system could operate via chemical signals that are used as social communication. This manipulation could benefit fitness of bacteria, such as reproduction and transmission and food cravings and preferences [32,33].

But despite some tantalizing evidence of social relationships influence on the gut microbiome, studies in human populations remain relatively small in number. Nonetheless, there is related evidence to support further exploration of connections between social relationships and the gut microbiome. There is growing empirical

support for links between social and physical environments. Humans sharing homes having more similar skin microbiomes compared to those not sharing a home, likely due to skin shedding, respiratory activity, and skin-surface contact [34]. When families moved, their microbial signature followed them to the new home, and individuals who left the home for several days saw a decline in their contribution to the home microbiome [34]. These findings suggest a mechanism for social transmission of bacterial communities through the built environment, which could apply to socially shared spaces such as schools, work, and public transportation. In light of this, as well as recent primate evidence that "immigrant" males share gut microbiome characteristics from both their birth and adult communities [35], life course residential and migration histories could play an important role in human microbiome dynamics.

Socioeconomic Conditions

Extensive research shows that adult socioeconomic resources, in addition to early life socioeconomic resources, influence morbidity and mortality. Life expectancy difference at age 25 can differ by as much as 16 years between those with the lowest and highest levels of educational attainment [36]. While there is little direct existing evidence linking adult socioeconomic resources to the gut microbiome, the link is highly plausible [12]. The gut microbiome is strongly implicated in metabolic and inflammatory disorders. Adult socioeconomic resources, in turn, pattern chronic inflammatory diseases and metabolic disorders, ranging from diabetes to heart disease. The prevalence of diabetes is twice as high among those with lower compared to higher educational attainment. Among those with diabetes and myocardial infarction, the mortality risk is substantially greater for those with lower educational attainment and incomes [37]. Moreover, there is a robust literature linking socioeconomic status to inflammatory markers, such C-reactive protein, more generally. To some extent, this pathway is linked via behaviors. In the U.S., obesity prevalence is 28 percent for women with a college degree compared to 45 percent for women without a high school degree [38]. Given the already robust evidentiary body linking diet to the gut microbiome, dietary behaviors may be a key path linking socioeconomic status to the gut microbiome.

In addition to possible behavioral pathways that could adult socioeconomic resources to the gut microbiome, there is emerging evidence of the role of psychosocial stress in modulating the microbiome [33,39,40]. This is important because psychosocial stress is a key pathway between many social environments (such as limited socioeconomic resources and social relationships) and morbidity and mortality outcomes [41]. Perhaps most striking is a study of bees that demonstrated position in their social hierarchies influenced the gut microbiome, with both diet and stress mediating these relationships [42]. Rodent models have convincingly shown that exposure to psychological stressors can alter the gut microbiome, through neuroendocrine response, the integrity of barrier defenses, and the internalization of microbes [43]. In mice, exposure to social stressors has been shown to alter homeostatic interactions between the intestinal microbiota and the immune system, leading to increased susceptibility to enteric infection, and overproduction of inflammatory mediators that induce anxiety-like behavior [44]. States of isolation, such as maternal neglect, appear to influence the gut microbial composition in animal models [45] at least in part through stress [43,46]. For example, in captive rhesus monkeys, maternal separation stress induced reductions in lactobacilli in intestinal microflora and higher rates of opportunistic enteric infection [45]. Prenatal stress in mothers has also been shown to impact the microbiota of offspring in mice, which in turn decreased the abundance of this bacterium in the gut microbiota of their offspring [47]. More generally, there is some evidence that maternal stress on child anxiety and mental health disorders may be modulated by the gut microbiome [47]. These alterations were subsequently related to changes in the offspring's metabolite profiles involved in energy balance, as well as with disruptions of amino acid profiles in the developing brain [47,48].

We do want to note that we have largely highlighted influences of social conditions on the microbiome. There is, however, empirical evidence supporting the idea that the composition of the microbiome may modulate individual behaviors, preferences, and choices and thus potentially shape individuals' social interactions and environments. If confirmed this bacterial "manipulation" of the human host has perplexing implications for the evolution of phenotypical traits. This is an active area of study, mostly with animal models,

and has already sparked controversy regarding the likely (or unlikely) sustainability of a strategy involving bacterial exploitation of their hosts [33].

The Need for Better Data

Overall, the existing evidence provides a strong rationale for the potential importance of social conditions for the dynamics of gut microbial composition across the life course, but thus far population-based evidence to confirm these relationships is limited. To move forward, the significant challenge of data availability needs to be addressed. While animal models have been invaluable in understanding the mechanisms underlying gut microbial composition and function, including the possible influence of social conditions, they are constrained by some important limitations—some of which are general issues with animal models, some specific to the study of the gut microbiome. First, the basic biological variance between mice (and some primates) and human models may limit the potential to translate what we learn about mice to humans [49,50]. Second, even if we overcome this challenge, animal studies are somewhat constrained in their ability to examine how more complex social phenomena, like human social relationships and networks, influence the gut microbiome. While we can draw useful parallels, similar to basic biological differences, the social and cognitive differences between humans and animals constrain comparisons.

Existing human studies also have some important limitations, especially if the goal is to explore how social environments influence the gut microbiome. Early human gut microbiome studies were constrained by small, non-randomly selected, samples. For example, the NIH directed and funded Human Microbiome Project (HMP) to map the healthy human microbiota in 2012 was conducted on a single non-random sample of 256 individuals from St. Louis and Houston, most of whom were researchers and students [51]. Despite the small number of non-whites in the HMP sample, comparisons were made across race/ethnicity (Asian, Black, Mexican, Puerto Rican, White), with the investigators reporting that a "wide variety of taxa, gene families and metabolic pathways were differentially distributed with subject ethnicity at every body habitat, representing the phenotype with the greatest number…of total associations with the microbiome [51]." These incidental findings of

strong associations with race/ethnicity suggest the need to characterize the microbiome in diverse, population-based samples. Yatsuneko, et al (2012) also highlighted the need for diverse samples, showing for the first time strong geographical differences in microbiome structure and function for residents of the US compared to the Amazon in Venezuela and rural Malawi.

More recently, there have been attempts to collect much larger samples [52], but these attempts fall far short both of population representativeness and measurement of the 'macroenvironment'. Voluntary crowdsourcing models such as The American Gut Project (AGP), (http://americangut.org) or UK-based MapMyGut (https://mapmygut.com) have been shown to be particularly non-representative. For example, only 6 percent of respondents in the AGP are obese compared to a 37 percent adult obesity rate overall in the U.S. [53]. As interest in the microbiome grows, larger studies are including microbiome collection. Key examples include the Belgian Flemish Gut Flora Project and the Dutch LifeLines Study [52,54]. Both studies include rich detail in regards to biological, anthropomorphic and general health data, however they contain more limited data on social environments—socioeconomic, family, work, and community—as compared to social and demographic based population health studies. Moreover, participants were not randomly selected, but rather were recruited through media campaigns, thus introducing selection and sample bias. The TwinsUK Study, one of most prolific of human studies of the gut microbiome thus far, was designed with a specific biomedical focus on the heritability of common diseases, with only superficial attention to the social environment. The disproportionately female and white volunteer sample does not reflect the race/ethnic and socioeconomic diversity of the overall UK population [55-62]. Importantly, the highly selected nature of these samples limits variation in both the microbial exposures and phenotypic outcomes of interest, reducing their analytical potential and ultimately their scientific generalizability.

What are the implications of non-representative samples in this emerging science? One related cautionary tale comes from the neuroscience of brain development. This research has largely been conducted on non-representative 'convenience' samples of volunteers, leading some to argue that these study findings

may be skewed [63]. A recent study supports this contention. Researchers compared a representative and non-representative sample of children in an imaging study focused on brain development; findings in data that better represented the population were markedly different than those in the unrepresentative sample showing a very different pattern of how differing regions of the brain develop as children age [64]. While this scenario may or may not repeat itself for existing microbiome and health research, it will be important to be aware of the heterogeneity of associations across different populations and how and why this variation may arise.

Collaborative Opportunities with Population Health Sciences

Given existing limitations, in this section we detail ways in which existing population based studies and methods could be employed to test novel hypotheses about social environments and the gut microbiome. But to start, we want to emphasize the broader potential methodological contributions that population health scientists might make to this field. One of the central challenges of human microbiome research, much like basic social science research, is how to demonstrate causal relationships. While animal models provide a straightforward platform, in and of themselves, they are not sufficient to fully explore the social determinants of the gut microbiome. Observational human microbiome studies, however, can suffer from familiar issues related to unobserved confounding and causal inference.

Collaborations between life science and social and population health researchers, however, can draw upon a long history in the social sciences of methods to improve causal inference in observational data, including family based designs, natural or "quasi-experiments", as well as population-based field experiments [65]. Opportunities for such research designs require microbiome data from ongoing, preferably longitudinal, studies with rich social, environmental and phenotypic data on participants. Since the largest cost in obtaining data from a large representative population is drawing the sample frame and the initial enrollment of participants, we argue that adding microbiome to existing population surveys is the most cost-effective approach relative to designing new studies from scratch. Many long-running population based studies (e.g. the Panel Study of Income Dynamics) follow families, which would allow for testing for intergenerational effects. Most large

longitudinal population based surveys also already collect biological data, ranging from blood to saliva. This would allow microbiome analysis in conjunction with high quality health data (including genetic and epigenetic data), while also leveraging the experience of these studies in getting their participants to provide these types of more sensitive data [66].

An ideal study design to investigate some of the pathways alluded to above should satisfy three conditions. First, as most population studies aspire to be, it should representative of a target metapopulation rather that based on highly selected samples which preclude more than modest generalization of inferences. Second, it should be flexible enough to maximize opportunities to make genuine causal statements rather that being a source of association measures which, in most cases, cannot be elevated to the status of estimates of causal effects, e.g. uncontaminated by omitted variable biases/confounding or selection mechanisms of various types. Third, because many of the relations portrayed in Figure 1 are a function of lags and delayed impacts, the ideal study should be longitudinal and a source of information on events that unfold over multiple stages in the life course of individuals.

Early Life Conditions

Over the last 10 to 15 years, research on the Developmental Origins of Adult Health and Disease (DOHaD) has produced robust empirical evidence suggesting the prenatal and early postnatal exposures have a strong influence on early growth and development and, under some conditions, have significant delayed impacts on adult health outcomes [67-71]. The first three years of life are crucial for colonization of the gut microbiome [72,73]. This points to the configuration of the microbiome as one pathway through which early conditions may operate, calling for social and population health scientists working under the DOHaD paradigm to explicitly include investigation of the microbiome over the life course.

Both bodies of research confront remarkably similar problems such as the existence of critical and sensitive periods, accumulation of damage and synergies over the life course, path dependencies, and reversibility properties [41,74-77]. It is likely that these problems, to which DOHaD and microbiome researchers

have arrived independently, might have common solutions. Moreover, both groups are pointing to epigenetic modifications as an important mechanism through which embryonic and prenatal exposures, on one hand, and composition of the microbiome, on the other, may sometimes operate [71,78-81].

While there are many examples of potentially fruitful joint research, an area that offers promise of very immediate rewards concerns the effects of early nutritional status and nutritional shocks on growth, development and adult health outcomes. Barker's seminal research implicated fetal nutritional impairments as an important determinant of adult chronic conditions, including obesity, coronary heart disease and Type 2 Diabetes, whereas a large literature in population health sciences investigates the effects of infant and child nutrition on diseases in adult mortality and disability (for a review see [82]). Until recently, this body of research made no reference to the relation between nutrition and microbiome. New research suggests that a paradigmatic shift is in order. A study of Malawian malnourished infants demonstrated, via fecal transplantation in mice, that 'gut microbial immaturity is causally related to child malnutrition" as "immature microbiota transmit impaired growth, altered bone morphology, and metabolic abnormalities…"[83]. This could be a smoking gun, as it shows that the microbiome is one mechanism that mediates the association of prenatal or neonatal malnutrition and later morbidity and mortality. If replicated, it provides a heretofore unknown and modifiable pathway.

Establishing relations involving the microbiome may also be required to fully understand other processes identified by DOHaD (and variants), such as those relating early exposure to acute stress and later mental health [84-86], childhood poverty and adversity to late onset of chronic illnesses [87-89], exposure to shocks such as influenza, natural disasters, wars to a broad array of chronic ailments [90], or recurrent childhood or adolescent infectious diseases, sustained inflammation, and later heart and circulatory [91-94].

But how can we explore these questions? One approach involves exploiting quasi experimental conditions generated by famines, including the Dutch Famine [95] and the Great Chinese Famine [96], which produce quasi randomly selected subpopulations exposed and unexposed to a "treatment". Studies of the Dutch famine

have uncovered, in samples of mid-life and older adults, that those exposed to the famine in utero, compared to those in utero in the months just preceding the famine, have everything from higher mortality rates from cardiovascular diseases to differences in DNA methylation [97-99] linked to metabolic health and transgenerational impacts on metabolic health. Differences in DNA methylation explained a significant portion of the differences in metabolic health between those with and without exposure to the famine in utero. Data on the gut microbiome could be added to these existing cohorts, with people currently in their 60s (Great Chinese Famine) and 70s (Dutch Famine). This could elucidate relations conjectured by DOHaD.

Though less common, RCTs, or field experiments are also being conducted to measure the impact of social interventions on health outcomes in larger population based samples. For example, a newly launched randomized (conditional) cash transfer experiment is enrolling one thousand infants, to track how a randomly assigned increase in income ($333 a month) affects cognitive development in poor children [100]. A wealth of longitudinal and quasi-experimental research points strongly to the influence of poverty on maternal stress and mental health, as well as the infants' cognitive development in early life. The addition of data on the gut microbiome would allow for the testing of the role of the gut microbiome as a mediator in these relationships. As already previously detailed, studies showing connections between the gut microbiome, maternal stress, and cognitive development would suggest these are pathways worth exploring.

Furthermore, there are a growing number of studies that involve controlled interventions that monitor large populations over extended periods of time. Thus, studies built around cash transfers programs, such as Progresa in Mexico, have become an ideal study design that many other low to middle income countries are following, thus generating massive data sets on a multiplicity of conditions and outcomes [101,102]. In addition, international organizations such as the World Bank, IFPRI, BID, and WHO periodically initiate studies that involve a multiplicity of social protection interventions and are designed to facilitate causal inference. Experiments involving cash transfers or those based on nutritional interventions could add a module to collect information on

pregnant women, maternal health and nutrition, peri and postnatal birth exposures, microbiota composition and various childhood outcomes.

Lastly, although the empirical evidence is still too fragile to confirm them, DOHaD and related theories pose conjectures involving transgenerational effects of some significance. To the extent that these may be contingent or directly influenced by changes in the microbiome, there will be ample room to test evolutionary biology hypotheses about the development (and disappearance) of phenotypical traits with strong impacts on reproduction and longevity. Thus, large population studies with the characteristics described above will not only be useful to population health scientists, but could have potential large spill over effects benefitting the growth of other disciplines.

Socioeconomic Conditions

Social and population health scientists have spent decades gathering and analyzing data that demonstrates that socioeconomic markers, such as education, income and wealth matter a great deal for adult health and mortality, as we detailed earlier [103]. Evidence linking behavioral factors, like obesity, and psychosocial stress, to both the gut microbiome and socioeconomic health disparities, provide a plausible basis for testing whether adult socioeconomic resources influence the gut microbiome [14, 15, 39, 101] To date, however, there is virtually no work exploring the potential of gut microbial composition as a biological mechanism linking adult SES to morbidity and mortality outcomes.

Existing population based longitudinal studies that have documented the influence of income and educational attainment on morbidity and mortality are large in number and increasingly include a wide array of more basic biological data collected from saliva, blood and even urine, hair and nail samples [104]. The addition of microbial data, then, would be a natural extension. These studies follow large populations of cohorts for extended periods of time and are a source of very rich information. Examples include the Health and Retirement Study (HRS), and its sister studies around the world, the National Study of Adult and Adolescent Health (AddHealth), and the British Cohort Studies.

Although these studies are not designed to be experimental, changing exogenous conditions sometimes induce a quasi-experimental set up that can be exploited. For example, the HRS in the United States has provided rich information on the effects of the Great Recession on individual health status changes [105]. The HRS, in addition to many other population based studies, has been used to test the influence of changes in schooling laws, as a source of exogenous change, on health, with outcomes ranging from diabetes and strokes to later life cognitive decline and mortality [104-105]. Many studies, including the HRS and AddHealth, now include genetic data, which allow for a Mendelian randomization approach—drawn from genetic variants linked to educational attainment—to test the causal influence of educational attainment on health [106-108]. Many of these studies could be replicated to test the influence of these exogenous changes on microbial composition, for example.

Combining animal experiments with insights from the kinds of observational human data detailed above may offer an especially unique methodological strategy to strengthen causal findings. There is, of course, already precedence for this. For example, a well-known study found that the transplantation of gut microbiota from obese humans to lean germ free recipient mice transfers an increased adiposity phenotype relative to transplants from lean donors [79]. This approach relies on hybrid human/animal studies to produce a robust causal design. They first find associations between phentoypes (like obesity in this case) and the composition of the gut microbiome and then they use animal models (with human fecal samples) to further test the causality of that associational relationship. For example, we know the chronic inflammatory conditions, like diabetes, are more deadly for those with low compared to high educational attainment, even after accounting for BMI [37]. Fecal transplants drawn from those with Type 2 diabetes, but who varied in their educational attainment and were comparable on characteristics like BMI could then be transplanted into mice to see how the gut microbiota influenced morbidity and mortality outcomes in these models. Is the gut microbiome a biological mechanism that can help clarify why lower levels of educational attainment are so harmful for health?

Social Relationships

Social and behavioral scientists have also shown that quality, quantity and duration of intimate contact and social relations are important for health, potentially as a buffer from stress. (For reviews see [109,110]). Across a wide array of empirical designs, ranging from animal models to human longitudinal studies and randomized controlled trials, the relationship between social relationships and health and mortality is the most well documented among specific social conditions that influence health and mortality [111]. Indeed, a recent review found that social relationships are a stronger predictor of mortality than is smoking [111]. Limited social interactions may contribute to reduced diversity in gut microbial communities among older persons or the socially isolated, another plausible biological mechanism for these strong associations of social relationships and health. As already detailed, there is some evidence from primate models, that social relationships, perhaps in part via direct microbial sharing, exerts an influence on gut microbial composition. Indeed, a recent study demonstrated that the oral microbiome infiltrates the gut microbiome, supporting evidence for microbial exchange via salivary mechanisms [112]. This area is ripe for study in human models to further test and elucidate pathways between social interactions, gut microbial composition and morbidity and mortality outcomes.

Our recent data collection in the Wisconsin Longitudinal Study (WLS) took a step in the direction of integrating social and biological approaches to the gut microbiome. This cohort of nearly 10,317 1957 Wisconsin high school graduates, their spouses and a subsample of siblings [113] has been followed the past 60 years and includes extensive social and phenotypic measurement of everything from high school records, education and occupation histories, to childhood conditions, health status, cognition, disability, mortality, and genetic data. Fecal samples from a randomly selected subsample of 436 participants were recently collected, targeting a mixture of sibling and spousal pairs in their mid-70s [66].

Because the subsample includes siblings as well as spouses, most of whom have been married and lived together their nearly entire adult lives, we were able to compare microbiome composition among those who share environments due to living arrangements across most of their adult lives to those who share only early upbringing conditions. We found [114] that shared environments in adult life had a stronger influence on microbial

389 composition in later life than did shared early life environments. This provided a mechanism to test the relatively
390 plasticity of the gut microbiome in population-based data. We also found that the similarity between spouses,
391 as compared to unrelated individuals, was entirely driven by married couples who reported they had a very
392 close relationships; in short, the shared gut microbial composition of married couples who rated their
393 relationship as "somewhat" good was similar to that of unrelated individuals.

394 Modest as it may be, this finding alone is important, for it generates new questions and problems. First,
395 it is somewhat unexpected given extant empirical evidence that points to the early colonization and stable
396 character of the microbiome [3]. Second, it confirms other findings in epidemiology according to which
397 environments shared by siblings explain only a small fraction of adult outcomes [115]. Finally, one puzzle to resolve
398 is whether or not the impact of shared environments by spouses on the microbiome is part of a chain of events
399 that accounts for within couple similarity in chronic illness [116].

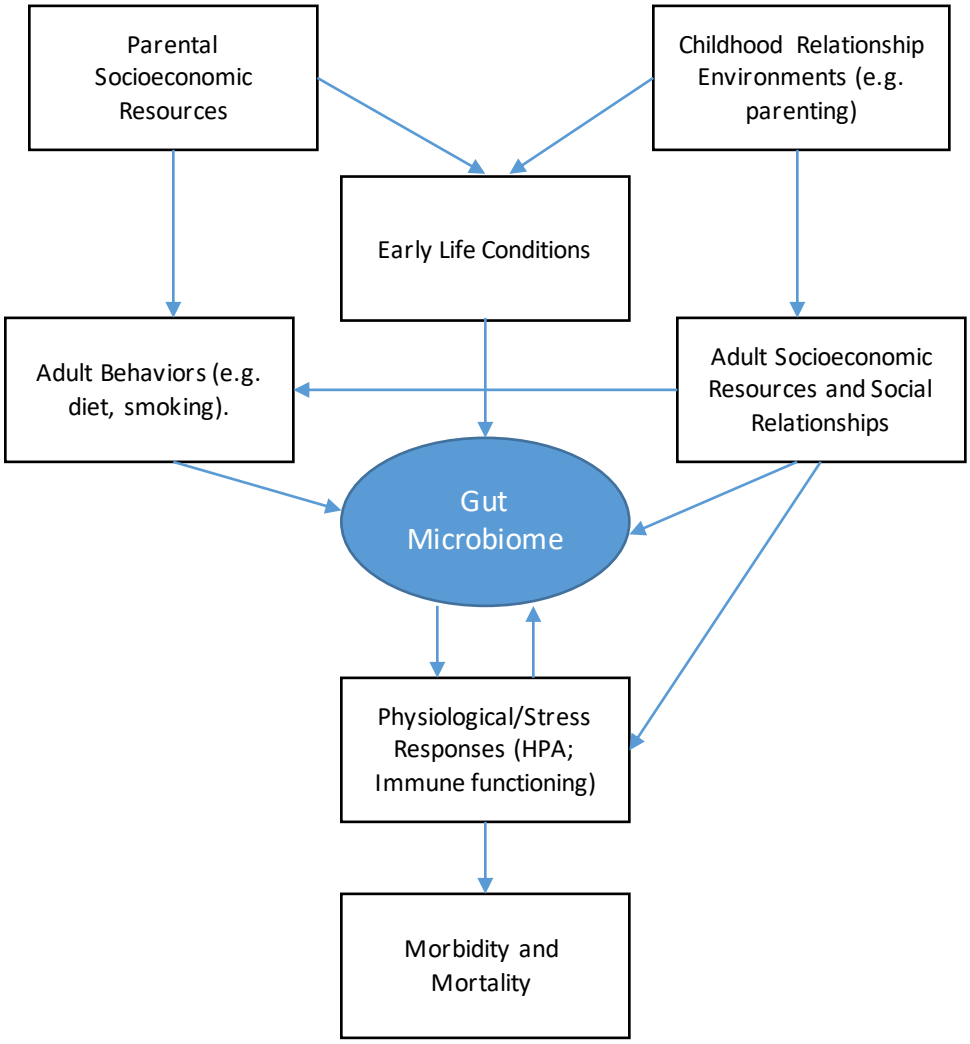
400 **Conclusion**

401 We believe these early days of microbiome research offer exciting opportunities for collaborations between the
402 life sciences and the social and population health sciences, a time when theory and measurement in both realms
403 is still developing and before disciplinary conventional wisdom has the chance to solidify. For social and
404 population health scientists, the study of the microbiome may help elucidate currently unknown biological
405 pathways that link social conditions to health and mortality, and provide a target for intervention.

406 For biologists, collaborations with social and population health scientists can enhance knowledge of a
407 new range of environmental factors that may influence microbial composition and, in turn, health. Insights from
408 the social and behavioral health research can also help contextualize existing findings. For example, the robust
409 evidentiary base linking diet and the gut microbiome should be considered in the context of broader population
410 health research that documents how structural conditions, ranging from economic resources to neighborhood
411 environments, constrain nutritional choices individuals make.

Both fields will benefit from the joining of social science and basic biological methodological approaches. Embedding animal models in the context of population based studies provides a novel approach to improving causal methods for social and population scientists. Having access to large, population representative, longitudinal based studies with high quality phenotypic measures can vastly expand the quality of research produced by biologists. Success will ultimately be measured by the ability of scientists across all disciplines to understand how the microbiome influences human health and social trajectories (and vice versa), and how social and medical interventions may use this knowledge to improve both individual well-being and population health.

Figure 1. Proposed Relationships between Social Conditions, the Gut Microbiome, and Morbidity and Mortality



Note: This figure is not intended to be a comprehensive overview of all possible causal relationships. It suggests where social and population health scientists are best positioned to contribute to microbiome research, focusing especially on the possible pathways between social conditions and the gut microbiome.

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Competing Interests

The authors declare that we have no competing interests as defined by Nature Research, or other interests that might be perceived to influence the results and/or discussion reported in this paper.